REMARKS

Claims 1-5 are pending in the instant application. Claims 2, 4 and 5 have been withdrawn from consideration. Claims 1 and 3 have been rejected. Claims 2, 4 and 5 have been canceled. Claims 1 and 3 have been amended. Applicants respectfully request reconsideration in view of the amendments to the claims and the following remarks.

I. Restriction Requirement

The Restriction Requirement placing claims 1 and 3 into Group I, claim 2 into Group II, claim 4 into Group 4, and claim 5 into Group IV, has been deemed Proper and made Final. Further, the Examiner has acknowledged Applicants election of Group I, claims 1 and 3, and fenretinide as the species. Accordingly, Applicants have canceled claims 2, 4 and 5 without prejudice, reserving the right to file continuing applications on the canceled subject matter.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1 and 3 have been rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The Examiner acknowledges that the specification as filed is enabling for "reducing a pro-inflammatory response in a diseased cell of the respiratory tract comprising contacting the cell with fenretinide", however, the Examiner suggests that the specification does not enable use of any agent that increases

ceramide levels in any diseased cell. Applicants respectfully traverse this rejection.

At the outset, in an earnest effort to advance the prosecution and facilitate allowance of the claims, Applicants have amended claims 1 and 3 to recite that the method of the present invention comprises administration of fenretinide and that the cells contacted are respiratory cells. Support for these amendments to the claims can be found throughout the specification as filed and is acknowledged by the Examiner in the statement of enablement above. Accordingly withdrawal of the rejection of claims 1 and 3 is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Dahl et al. (U.S. Patent Application No. 2003/0216471). The Examiner suggests that this patent application discloses the treatment of diseases of the aerodigestive tract, such as emphysema, COPD, and inflammation, with retinoids such as fenretinide. The Examiner admits that the patent application fails to teach or suggest use of fenretinide specifically to inhibit pro-inflammatory responses in a diseased cell, as claimed in claim 1. However, the Examiner suggests that it would have been obvious to use fenretinide as claimed because Dahl et al. teaches that retinoids, including fenretinide, treat respiratory diseases and inflammation upon contact. Further, the Examiner suggests that increasing ceramide levels is an inherent property of the compound. Applicants respectfully disagree with the Examiner's conclusions regarding this prior art reference.

Dahl et al. (2003/0216471) disclose retinoid formulations for aerosolization and inhalation and their use to treat respiratory disease, in particular cancer. The patent application provides data showing that all-trans retinoic acid (ATRA) and related natural retinoids have activity to affect cancer cell growth and potentially prevent cancer. Although the patent application dose mention treatment of inflammation with retinoid compounds, as well as mentioning the synthetic compound fenretinide as one compound in a general list of retinoid compounds, the patent application fails to provide any working example of use of fenretinide in any cell or animal, including respiratory cells. Moreover, nowhere does this patent application teach or even suggest use of any retinoid to treat a pro-inflammatory condition as claimed in claim 1 of the instant application. Therefore, nowhere does this prior art reference provide any actual data showing that fenretinide has activity to treat inflammation and as such one of skill in the art would have no expectation of success then in using fenretinide to inhibit or reduce a pro-inflammatory response in a diseased respiratory cell as claimed. Although the Examiner has stated that MCF-7 cells were contacted with a retinoid, and relies on that fact to support the case of obviousness, the retinoid used in the patent application is NOT fenretinide, but is instead either ATRA or 13-cis-RA, and further MCF-7 cells are breast cancer cells, not diseased respiratory cells.

What is important to realize, is that at the time the application was filed in 2006, it was well known in the prior art that fenretinide had a distinct pharmacological profile from other retinoic acid compounds. Fenretinide, a synthetic retinoid

compound, has been discussed in many published articles as having a pharmacological and toxicological profile distinct from ATRA and other naturally-occurring retinoids (*e.g.*, Ulukaya and Wood. 1999. *Cancer Treat Rev.* 25:229-235; Hail *et al.* 2006. *Apoptosis* 11:1677-1694). In fact, it was known in the literature prior to the filing date of the instant application that fenretinide induces its effects in cancer mainly through retinoid receptor-independent mechanisms, while ATRA acts through retinoid receptor mechanisms (Simeone and Tari 2004. *Cell Mol. Life Sci.* 61:1475-1484). As a result, contrary to the Examiner's suggestions, one of skill in the art would NOT use teaching related to ATRA, such as taught by Dahl et al., to expect success using fenretinide in a any situation, since fenretinide has its own unique pharmacological profile. Clearly, it would also not be an inherent property of all retinoic compounds to affect ceramide levels as suggested by the Examiner. Moreover, the activity of fenretinide in respiratory cells to affect inflammation and pro-inflammatory conditions would not be predictable based on teachings of the activity of natural retinoid compounds such as ATRA in cancer cells. It is only with the specification in hand that one of skill in the art would be able to expect success at using fenretinide to affect a pro-inflammatory condition as claimed in instant claim 1.

MPEP 2143 states that in order to establish a *prima facie* case of obviousness the cited reference must teach the limitations of the claims as well as providing one of skill with both a motivation and an expectation of success in making and using the claimed invention. Clearly, the patent application of Dahl et al. fails to provide one of skill with an expectation of

success based on what was known about fenretinide prior to the fining of the instant application. Accordingly, the reference of Dahl et al. fails to establish a prima facie case of obviousness. However, in an effort to further distinguish the claimed invention of instant claim 1 from the art dealing with cancer treatment and retinoids, Applicants have amended claim 1 to recite that the diseased respiratory cell is a cell that is representative of the disease state of cystic fibrosis. Support for this amendment to claim 1 can be found throughout the specification as filed where the present invention is applied to cystic fibrosis and the investigation of lung cells with cystic fibrosis disease-related genetic defects. Withdrawal of this rejection is respectfully requested.

Claim 3 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Mathias et al. (1998) in view of Maurer *et al.* (1999). The Examiner suggests that Mathias *et al.* (1998) teach the signal transduction of stress via ceramide and that in macrophage cells in particular ceramide causes inflammation via the MAPK pathway. The Examiner acknowledges that Mathias *et al.* (1998) fails to teach or suggest that fenretinide induces an inflammatory response. The Examiner then suggests that Maurer *et al.* (1999) teaches that fenretinide increases ceramide in neuroblastoma cells. As a result, the Examiner suggests it would have been *prima facie* obvious for one of ordinary skill in the art to use fenretinide to specifically induce an inflammatory response in a cell because fenretinide increases ceramide as taught by Maurer *et al.* (1999) and ceramide induces inflammation as taught by Mathias *et al.* (1998). Applicants respectfully traverse this rejection.

In an earnest effort to advance the prosecution and facilitate allowance of the claims, Applicants have amended claim 3 to recite that the diseased respiratory cell is a cell that is representative of the disease state of cystic fibrosis. Support for this amendment to claim 3 can be found throughout the specification as filed where the present invention is applied to cystic fibrosis and the investigation of lung cells with cystic fibrosis disease-related genetic defects.

Mathias et al. (1998) is a review articles that discusses the role of ceramide in biological functions of cells. Although the reference teaches that ceramide functions in cells to affect cell proliferation, cell death, cell differentiation, and cell growth, only one aspect of ceramide's involvement with inflammatory processes is discussed, specifically its role in macrophages. Nowhere does this reference teach or suggest a role for ceramide to induce inflammation in respiratory cells and further nowhere does the reference teach or suggest the use of fenretinide to increase ceramide levels in respiratory cells or any type, including respiratory cells that are representative of the disease state of cystic fibrosis. Given the unique nature of cystic fibrosis as a disease and the fact that macrophages are not similar in any respect to such respiratory cells, one of skill in the art would not expect that increasing ceramide levels in macrophages would relate to activity of ceramide in such diseased respiratory cells. The teachings of Maurer et al. (1999) fail to overcome the deficiencies in teaching of Mathias et al. (1998). Maurer et al. (1999) teach that fenretinide increases ceramide levels in cancer cells, specifically neuroblastoma cells. However, this reference also fails to teach

or suggest the actions of ceramide or any agent that affects ceramide levels in respiratory cells or any type, including respiratory cells that are representative of the disease state of cystic fibrosis. The reference also fails to teach or suggest that ceramide in involved in induction of an inflammatory process in a respiratory cells that is representative of the disease state of cystic fibrosis. Again, given the unique nature of cystic fibrosis as a disease and the fact that neuroblastoma cells, which are cancer cells, are not similar in any significant respect to such respiratory cells, one of skill in the art would not expect that increasing ceramide levels in such cells with fenretinide would relate to activity of fenretinide in such diseased respiratory cells. MPEP 2143 states that in order to establish a *prima facie* case of obviousness the cited reference must teach the limitations of the claims as well as providing one of skill with both a motivation and an expectation of success in making and using the claimed invention. Clearly, the combination of prior art references cited by the Examiner fails to provide one of skill with an expectation of success for inducing an inflammatory response in a diseased cell representative of the disease state of cystic fibrosis as claimed in amended claim 3. Accordingly, these references fail to establish a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

IV. Conclusions

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claim is earnestly solicited.

Respectfully submitted,

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